Role of volume sensitive Ca permeable channel, TRPV4, in the kidney.

Makoto Suzuki

Jichi Medical School. Department of Pharmacology.

Summary

Transient receptor potential (TRP) is a molecular family of Ca permeable cation channels. TRPV4 is a family member similar to vanilloid receptor and only Ca permeable channel activated by the swelling of cell. We have first reported that impaired sensitivity to plasma osmolarity was observed in mice lacking TRPV4. Although the controversy remained in the regulation of body osmolarity, TRPV4 may play a role in renal electrolyte metabolism because mRNA is rich in the kidney. To access a contribution of TRPV4 to renal physiology, we investigated (1) in vitro the volume-sensitive intracellular Ca of renal tubules in response to aniso-osmolarity and (2) Na and K metabolism during various salt and diuretic intakes.

TRPV4 is located in basolateral membrane of thick ascending limb to collecting duct cells. We microdissected distal renal tubule with adjacent proximal tubule and measured the intracellular free calcium (iCa). The bath osmolarity was changed from hypertonic to hypotonic solution. The iCa decreased and them increased in distal tubule of TRPV4+/+ and proximal tubules in TRPV4+/+ and TRPV4-/- mouse. Whereas, iCa did not increase in the distal tubule of TRPV4-/- mouse. Thus swell-sensitive rise in iCa was impaired in TRPV4-/-.

Restriction or overdose of salt to mice in balanced cage resulted in that dairy urinary Na or K excretion and their concentrations were not different between TRPV4+/+ and -/- mice. Thus concentration of urinary Na is not primary signal to stimulate TRPV4. In other words, hypotonicity or hypertonicity of luminal fluid of the distal segments did not stimulate TRPV4 activation. Urinary Na/K concentration vs. urine volume, however, was different between these animals. Thus TRPV4 may sense urinary flow rather than urinary osmolarity. To clarify the issue, we added diuretics to 2% NaCl of tap water for drinking and found a significant difference in Na-UV or K-UV relationships in TRPV4+/+ and -/- mice. The relationships revealed linear, the increment of which were significantly different by two-way ANOVA.

We therefore conclude that TRPV4, a volume sensitive Ca permeable channel, senses flow rather than concentration of urine. The flow-dependent Na and K excretion mechanism may be impaired in mice lacking TRPV4.